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(54) Title: **METHODS AND COMPOUNDS FOR INHIBITING AMYLOID DEPOSITS**

(57) Abstract: Methods and compositions which are useful in the treatment of amyloidosis. In particular, methods and compositions are provided for inhibiting, preventing and treating amyloid deposition, e.g., in pancreatic islets, wherein the amyloidotic deposits are islet amyloid polypeptide (IAPP)-associated amyloid deposition or deposits. The methods of the invention involve administering to a subject a therapeutic compound which inhibits IAPP-associated amyloid deposits. Accordingly, the compositions and methods of the invention are useful for inhibiting IAPP-associated amyloidosis in disorders in which such amyloid deposition occurs, such as diabetes.

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METHODS AND COMPOUNDS FOR INHIBITING AMYLOID DEPOSITS

This application claims the benefit of priority under 35 U.S.C. 119(e) to copending U.S. Provisional Application No. 60/135,545, filed on May 24, 1999, and U.S. Provisional Application No. 60/143,123, filed on July 9, 1999, the entire contents of which are incorporated herein by reference. This application is also related to U.S. Patent No. 5,972,328, issued October 26, 1999, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

10 Amyloidosis refers to a pathological condition characterized by the presence of amyloid. Amyloid is a generic term referring to a group of diverse but specific intra- and extracellular protein deposits which are associated with a number of different diseases. Though diverse in their occurrence, all amyloid deposits have common morphologic properties, including that they stain with
15 specific dyes (e.g., Congo red), and have a characteristic birefringent appearance (sometimes characterized as "red-green") in polarized light after staining. They also share common ultrastructural features and common x-ray diffraction and infrared spectra.

Amyloidosis can be classified clinically as primary, secondary, familial
20 and/or isolated. Isolated forms of amyloidosis are those that tend to involve a single organ system. Different amyloids are also characterized by the type of protein present in the deposit. For example, neurodegenerative diseases such as scrapie, bovine spongiform encephalitis, Creutzfeldt-Jakob disease and the like are characterized by the appearance and accumulation of a protease-resistant form of a
25 prion protein (referred to as AScr or PrP-27) in the central nervous system. Similarly, Alzheimer's disease, another neurodegenerative disorder, is characterized by congophilic angiopathy, neuritic plaques and neurofibrillary tangles, all of which have the characteristics of amyloids. In this case, the plaque and blood vessel amyloid is formed by the beta protein. Other diseases, such as
30 juvenile and adult-onset diabetes, complications of long-term hemodialysis and

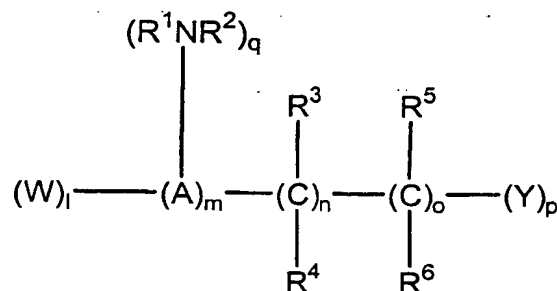
sequelae of long-standing inflammation or plasma cell dyscrasias are characterized by the accumulation of amyloids systemically. In each of these cases, a different amyloidogenic protein is involved in amyloid deposition.

Islet amyloid polypeptide (IAPP) is known to be capable of forming fibrils which are deposited in the pancreas of patients with Type II diabetes, forming deposits. Once these amyloid deposits have formed, there is no known therapy or treatment which significantly reduces or clears the deposits *in situ*.

SUMMARY OF THE INVENTION

This invention provides methods and compositions which are useful in the treatment of amyloidosis. In particular, methods and compositions are disclosed for inhibiting, preventing and treating amyloid deposition, e.g., in pancreatic islets wherein the amyloidotic deposits to be treated are, e.g., islet amyloid polypeptide (IAPP)-associated amyloid deposits having at least some β -sheet structure. The methods of the invention involve administering to a subject a therapeutic compound which inhibits, reduces or disrupts amyloid deposits, e.g., IAPP-associated amyloid deposits. Accordingly, the compositions and methods of the invention are useful for inhibiting amyloidosis in disorders in which such amyloid deposition occurs, such as diabetes.

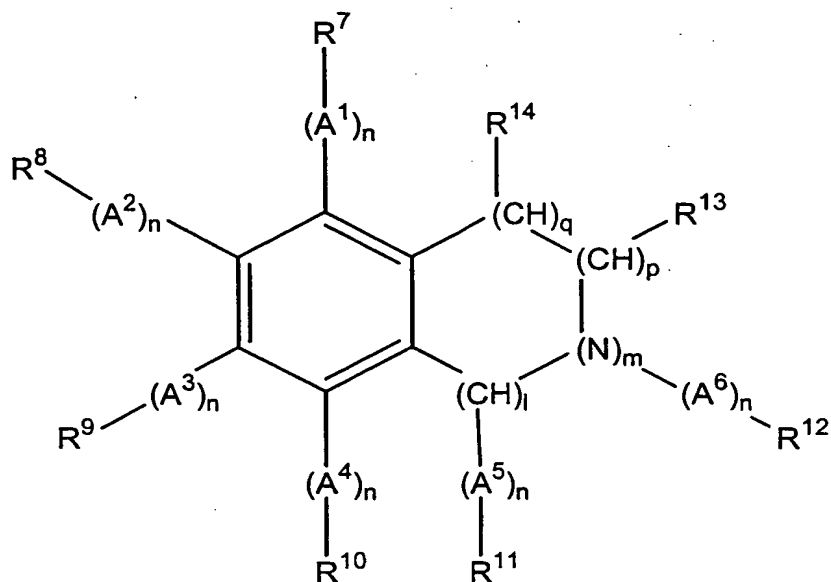
In one embodiment, a method for inhibiting amyloid deposition, particularly IAPP-associated amyloid deposition, in a subject is provided, wherein an effective amount of an IAPP-inhibiting compound, or a pharmaceutically acceptable salt thereof, is administered to the subject such that said IAPP-associated amyloid deposition is inhibited. Such compounds include those of the following general formula



wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological pH; Y is an anionic group at physiological pH; R¹ and R² are independently hydrogen, alkyl, an anionic group at physiological pH, or R¹ and R², taken together
5 with the nitrogen to which they are attached, may form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R³ is hydrogen, halogen, thiol or hydroxyl; R⁴, R⁵, and R⁶ are independently hydrogen or halogen; and A is hydrogen or C₁ to C₆ alkyl; or a pharmaceutically acceptable ester, acid or salt thereof.

10 Preferred therapeutic compounds include 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; 2-amino-5-phosphovaleric acid; 4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; *O*-phospho-*L*-serine; hexafluoroglutaric acid; 3-amino-2-hydroxy-1-propanesulfonic acid; 8-methoxy-5-quinolinesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, the
15 compounds depicted in FIGs 10-14, and pharmaceutically acceptable esters, acids or salts thereof.

In another embodiment a method for inhibiting amyloid deposition, particularly IAPP-associated amyloid deposition, in a subject is provided, wherein an effective amount of an IAPP-inhibiting compound, or a pharmaceutically
20 acceptable ester, acid or salt thereof, is administered to the subject such that said IAPP-associated amyloid deposition is inhibited. Such compounds include those of the following general formula



wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups (e.g., R^7 and R^8) may form an unsubstituted or substituted cyclic or heterocyclic ring. In an embodiment, R^{13} may be anionic.

Preferred therapeutic compounds include 1,2,3,4-tetrahydroisoquinoline, and the compounds depicted in FIGs 1-9.

10 In another embodiment the invention relates to a method for reducing IAPP-associated amyloid deposits in a subject having IAPP-associated amyloid deposits, the method comprising administering to a subject an effective amount of an IAPP inhibiting compound, or a pharmaceutically acceptable ester, acid or salt thereof, such that IAPP-associated amyloid deposits are reduced.

15 The therapeutic compounds of the invention are administered to a subject by a route which is effective for inhibiting IAPP-associated amyloid deposition. Suitable routes of administration include oral, transdermal, subcutaneous, sublingual, buccal, intravenous and intraperitoneal injection. The therapeutic compounds can be administered with a pharmaceutically acceptable vehicle.

The invention further provides pharmaceutical compositions for treating amyloidosis. The pharmaceutical compositions include a therapeutic compound of the invention in an amount effective to inhibit IAPP-associated amyloid deposition, and a pharmaceutically acceptable vehicle.

5 **BRIEF DESCRIPTION OF THE DRAWING**

Figures 1-14 depict exemplary chemical structures of compounds described in the specification.

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention will be more fully illustrated by reference to the definitions set forth below.

 “Amyloid” includes IAPP-associated amyloid, including, but not limited to, β -sheet amyloid assembled substantially from IAPP subunits. “Inhibition” of amyloid deposition includes preventing or stopping of IAPP-associated amyloid formation, e.g., fibrillogenesis, inhibiting or slowing down of further IAPP-
15 associated amyloid deposition in a subject with amyloidosis, e.g., already having amyloid deposits, and reducing or reversing IAPP-associated amyloid deposits in a subject with ongoing amyloidosis. Inhibition of amyloid deposition is determined relative to an untreated subject, or relative to the treated subject prior to treatment, or, e.g., determined by clinically measurable improvement in pancreatic function in
20 a diabetic patient.

 Pharmaceutically acceptable esters, acids or salts of the therapeutic compound, where applicable, are within the scope of the invention, e.g., alkali metal, alkaline earth metal, higher valency cation (e.g., aluminum salt), polycationic counter ion or ammonium salts. Where a compound is anionic, a
25 preferred pharmaceutically acceptable salt is a sodium salt. Other salts are also contemplated, e.g., HCl, citric acid, tartaric acid salts, within their pharmaceutically acceptable ranges.

 The therapeutic compound of the invention can be administered in a pharmaceutically acceptable vehicle. As used herein “pharmaceutically acceptable
30 vehicle” includes any and all solvents, dispersion media, coatings, antibacterial and

antifungal agents, isotonic and absorption delaying agents, and the like which are compatible with the activity of the compound and are physiologically acceptable to the subject. An example of a pharmaceutically acceptable vehicle is buffered normal saline (0.15 molar NaCl). Except insofar as any conventional media or agent is incompatible with the therapeutic compound, use thereof in the compositions suitable for pharmaceutical administration is contemplated. Supplementary active compounds can also be incorporated into the compositions.

An "anionic group," as used herein, refers to a group that is negatively charged at physiological pH. Preferred anionic groups include carboxylate, sulfate, sulfonate, sulfinatate, sulfamate, tetrazolyl, phosphate, phosphonate, phosphinate, and phosphorothioate or functional equivalents thereof. "Functional equivalents" of anionic groups include bioisosteres, e.g., bioisosteres of a carboxylate group. Bioisosteres encompass both classical bioisosteric equivalents and non-classical bioisosteric equivalents. Classical and non-classical bioisosteres are known in the art (see, e.g., Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, Inc.: San Diego, CA, 1992, pp.19-23). A particularly preferred anionic group is a carboxylate.

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), and more preferably has 20 or fewer carbon atoms in the backbone. Likewise, cycloalkyls may have from 4-10 carbon atoms in their ring structure, more preferably have 5, 6 or 7 carbons in the ring structure.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate,

alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, 5 sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, e.g., with the substituents 10 described above. An "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)).

The term "aryl" herein includes 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, tetrazole, pyrazole, 15 pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl groups also include polycyclic fused aromatic groups such as naphthyl, quinolyl, indolyl, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as 20 described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including 25 alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

The terms "alkenyl" and "alkynyl" include unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

Unless the number of carbons is otherwise specified, "lower alkyl" means
5 an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls.

The terms "heterocyclyl" or "heterocyclic group" include 3- to 10-
10 membered ring structures, more preferably 4- to 7- membered rings, which ring structures include one to four heteroatoms. Heterocyclyl groups include pyrrolidine, oxolane, thiolane, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such
15 substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino
20 (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety.

The terms "polycyclyl" or "polycyclic group" include two or more cyclic
25 rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl,
30 alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy,

carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido),
5 amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

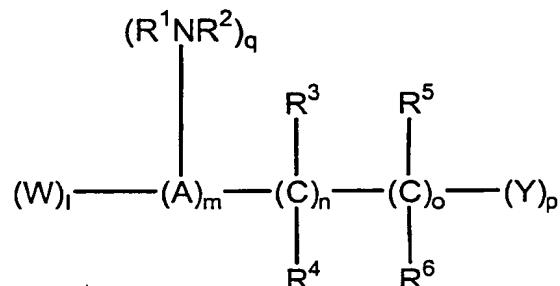
10 The term "aryl aldehyde," as used herein, includes compounds represented by the formula Ar-C(O)H , in which Ar is an aryl moiety (as described above) and -C(O)H is a formyl or aldehydo group.

It will be noted that the structures of some of the compounds of this invention include asymmetric carbon atoms. It is to be understood accordingly that
15 the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, alkenes or alkynes can include either the E- or Z- geometry, where appropriate.

20 The present methods and compositions, in embodiments, inhibit, prevent and treat amyloid deposition in pancreatic islets wherein the amyloidotic deposits to be treated are islet amyloid polypeptide (IAPP)-associated amyloid deposits, e.g., having at least some β -sheet structure. The methods of the invention include administering to a subject a therapeutic compound which inhibits, reduces or
25 disrupts IAPP-associated amyloid deposits. Accordingly, the compositions and methods of the invention are useful for inhibiting amyloidosis in disorders in which such amyloid deposition occurs, such as diabetes.

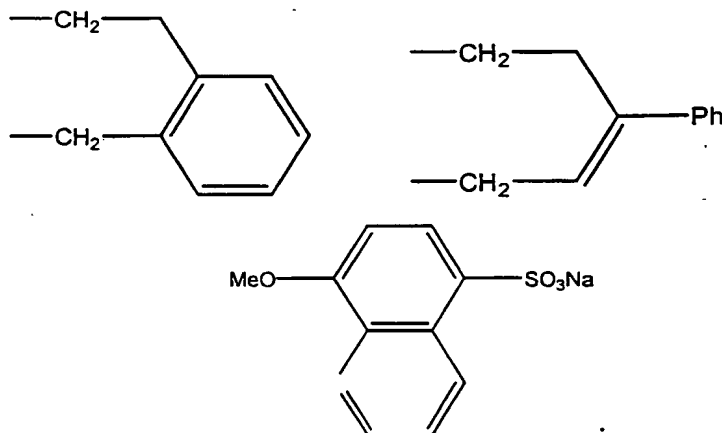
In one embodiment, a method for inhibiting IAPP-associated amyloid deposition in a subject is provided, wherein an effective amount of an IAPP-
30 inhibiting compound, or a pharmaceutically acceptable ester, acid or salt thereof, is

administered to the subject such that said IAPP-associated amyloid deposition is inhibited. Such compounds include those of the following general formula:



wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or
 5 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological
 pH; Y is an anionic group at physiological pH; R¹ and R² are independently
 hydrogen, alkyl, an anionic group at physiological pH, or R¹ and R², taken together
 with the nitrogen to which they are attached, may form an unsubstituted or
 substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R³ is
 10 hydrogen, halogen, thiol or hydroxyl; R⁴, R⁵, and R⁶ are independently hydrogen or
 halogen; and A is hydrogen or C₁ to C₆ alkyl; or a pharmaceutically acceptable
 ester, acid or salt thereof.

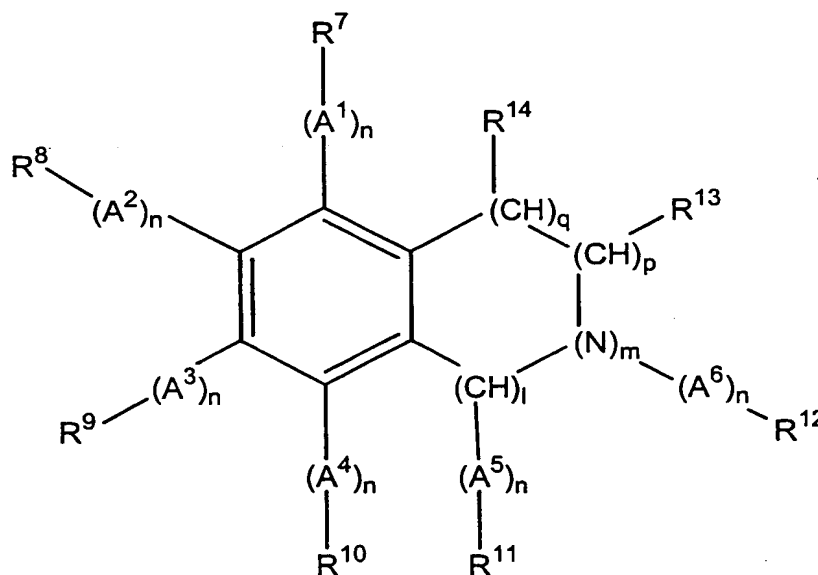
In an embodiment, W is preferably -COOH; Y is preferably -COOH, -
 SO₃H, -PO₃H₂, or -OP(O)(OH)₂; R¹ is preferably H, Me or hydroxypropyl; R² is
 15 preferably H, Me or -SO₃H; R₃ is preferably H, F, or OH; when R¹ and R², taken
 together with the nitrogen to which they are attached, form an unsubstituted or
 substituted heterocycle, preferred groups include



R^4 , R^5 and R^6 are preferably H or F; A is preferably H, CH, CF_2 or alkyl which may be substituted or unsubstituted, straight, branched or cyclic, e.g., cyclohexyl.

Preferred therapeutic compounds include 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; 2-Amino-5-phosphovaleric acid; 4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; O-phospho-L-serine; hexafluoroglutaric acid; 3-amino-2-hydroxy-1-propanesulfonic acid; 8-methoxy-5-quinolinesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, the compounds depicted in FIGs 10-14, and pharmaceutically acceptable esters, acids or salts thereof.

In another embodiment, a method for inhibiting IAPP-associated amyloid deposition in a subject is provided, wherein an effective amount of an IAPP-inhibiting compound, or a pharmaceutically acceptable ester, acid or salt thereof, is administered to the subject such that said IAPP-associated amyloid deposition is inhibited. Such compounds include those of the following general formula:



wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups (e.g., R^1 and

R²) may form an unsubstituted or substituted cyclic or heterocyclic ring. In an embodiment, R¹³ may be anionic.

Preferred therapeutic compounds include 1,2,3,4-tetrahydroisoquinoline, and the compounds depicted in FIGs 1-9.

5 A further aspect of the invention includes pharmaceutical compositions for treating amyloidosis. The therapeutic compounds in the methods of the invention, as described hereinbefore, can be incorporated into a pharmaceutical composition in an amount effective to inhibit amyloidosis or reduce amyloid deposits, in a pharmaceutically acceptable vehicle.

10 In the methods of the invention, amyloid deposition in a subject is inhibited by administering a therapeutic compound of the invention to the subject. The term subject includes living organisms in which amyloidosis can occur. Examples of subjects include humans, apes, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. Administration of the compositions of the present
15 invention to a subject to be treated can be carried out using known procedures, at dosages and for periods of time effective to inhibit amyloid deposition or reduce amyloid deposits in the subject. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the amount of amyloid already deposited at the clinical site in the subject, the age, sex,
20 and weight of the subject, and the ability of the therapeutic compound to inhibit amyloid deposition or reduce amyloid deposits in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

25 The active compound may be administered by routes such as oral, sublingual, buccal, transdermal, subcutaneous, intravenous, and intraperitoneal administration. Depending on the route of administration, the active compound may be coated in a material to protect the compound from the action of acids, enzymes and other natural conditions which may inactivate the compound.

The compounds of the invention can be formulated to ensure proper distribution *in vivo*. For example, the therapeutic compounds of the invention can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Patents 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs ("targeting moieties"), thus providing targeted drug delivery (see, e.g., V.V. Ranade (1989) *J. Clin. Pharmacol.* 29:685). Exemplary targeting moieties include folate or biotin (see, e.g., U.S. Patent 5,416,016 to Low *et al.*); mannosides (Umezawa *et al.*, (1988) *Biochem. Biophys. Res. Commun.* 153:1038); antibodies (P.G. Bloeman *et al.* (1995) *FEBS Lett.* 357:140; M. Owais *et al.* (1995) *Antimicrob. Agents Chemother.* 39:180); surfactant protein A receptor (Briscoe *et al.* (1995) *Am. J. Physiol.* 1233:134); gp120 (Schreier *et al.* (1994) *J. Biol. Chem.* 269:9090); see also K. Keinanen; M.L. Laukkanen (1994) *FEBS Lett.* 346:123; J.J. Killian; I.J. Fidler (1994) *Immunomethods* 4:273. In a preferred embodiment, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.*, (1984) *J. Neuroimmunol.* 7:27).

The therapeutic compound may also be administered parenterally, sublingually, buccally, intraperitoneally, intraspinally, or intracerebrally. Dispersions can be prepared in, e.g., glycerol, liquid polyethylene glycols, and mixtures thereof, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

- Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like.
- In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.
- Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yield a powder of the active ingredient (i.e., the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, sublingual/buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of amyloid deposition in subjects.

Active compounds are administered at a therapeutically effective dosage sufficient to inhibit amyloid deposition in a subject. A "therapeutically effective dosage" preferably inhibits amyloid deposition and/or reduces amyloid deposits by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects or to the same subject prior to treatment.

The ability of a compound to inhibit amyloid deposition or reduce amyloid deposits can be evaluated in an animal model system that may be predictive of efficacy in inhibiting amyloid deposition or reducing amyloid deposits in human diseases. The ability of a compound to inhibit amyloid deposition can also be

evaluated by examining the ability of the compound to inhibit amyloid deposition *in vitro* or *ex vivo*, e.g., using an ELISA assay. The effect of a compound on the secondary structure of the amyloid can further be determined by thioflavine T (ThT) assay, circular dichroism (CD) or infrared (IR) spectroscopy.

5 CD and IR spectroscopy are particularly useful techniques because the information obtained is a direct measure of the ability of a test compound to prevent or reverse amyloidosis, by determining the structural effect of a compound on amyloid protein folding and/or fibril formation. This contrasts with previously known methods which measure cellular trafficking of amyloid protein precursors
10 or interactions between amyloid and extracellular matrix proteins, providing only indirect evidence of potential amyloid-inhibiting activity. It should further be noted that CD and IR spectroscopy can also detect compounds which cause an increase in, e.g., β -sheet folding of amyloid protein, and thereby stabilize the formation of amyloid fibrils.

15 The deposition of amyloid is a multi-stage process. Accordingly, an agent useful for treating amyloidosis has many potential modes of action. An agent which inhibits amyloid deposition could act in one or more of the following ways, which are shown by way of illustration and not limitation:

1. Inhibition or delay of protein folding in solution;
- 20 2. Inhibition or delay of aggregation/elongation of oligomerized amyloid peptides into fibrils and/or deposits; and
3. Disruption/dissolution/modification of amyloid fibrils and/or deposits;

Categories 1 and 2 correspond to prevention of the formation of amyloid
25 deposits (slowing down or halting amyloid deposition), and category 3 corresponds to removal or modification of deposits already formed (removal or reduction of existing amyloid deposits).

The invention is further illustrated by the following examples which should not be construed as further limiting the subject invention.

EXAMPLE 1

Determination of the rate of amyloid fibril formation by Thioflavine T spectroscopy

Thioflavine T (ThT) binds to amyloid proteins in β -sheet formation, exhibiting a yellow fluorescence from tissue sections and fibrils *in vitro*. Detection of ThT fluorescence can be used as a sensitive assay for amyloid fibril formation under different conditions. This assay has been used in experiments to determine the effects of compounds of the invention on amyloid fibril formation.

Method

Synthetic human IAPP (Bachem) was dissolved in 40% trifluoroethanol and freeze-dried into conveniently-sized aliquots. IAPP was prepared immediately before the measurements by dissolving in 40% 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in water to maintain the peptide in alpha helical conformation and soluble. A stock solution of ThT (2.5mM) was prepared, 7.9mg in 10mL Tris-HCl pH 7.0 and filtered (0.22 μ m). Solutions were kept in the dark until use. Fluorescence was examined at 440nm excitation (slit 5nm), and emission at 482nm (slit 10nm) with stirring. 25ml of ThT stock (final concentration 62.5 μ M) was added to peptide sample and made up to 1mL in the cuvette. The sample was stirred for 5 min. before taking a reading. Measurements were made at an initial time point (5 min. from sample preparation), at intervals over the next 4-6h and after overnight incubation at room temperature.

Certain compounds (or their salts, as noted) as disclosed herein, i.e., 3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid; 2-amino-5-phosphovaleric acid; 4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine; cyclohexylsulfamic acid; O-phospho-L-serine; hexafluoroglutaric acid; 8-methoxy-5-quinolinesulfonic acid; 3-amino-2-hydroxy-1-propanesulfonic acid; and 3-dimethylamino-1-propanesulfonic acid, and 1,2,3,4-tetrahydroisoquinoline, were found, using this assay, to inhibit or prevent IAPP-associated fibril assembly.

EXAMPLE 2

Circular dichroism analysis was conducted to confirm the activity of certain therapeutic compounds in preventing or inhibiting IAPP-associated fibril formation in accordance with the present disclosure by determining the presence or absence of β -sheet conformation. The results are presented in Table 1.

The assay is conducted as follows:

INSTRUMENT AND PARAMETERS

Instrument: JASCO J-715 Spectropolarimeter
Cell/cuvette: Hellma quartz (QS) with 1.0 mm pathlength
Room temperature
Wavelength interval: 250 nm-190 nm
Resolution: 0.1 nm
Band width: 1.0 nm
Response time: 1 sec
Scanning speed: 20 nm/min
Number of spectra run: 5

The assay, a co-incubation procedure, examines the ability of a compound or substance to inhibit the assembly of amyloid fibrils, e.g., to test for the presence of the amyloidotic β -sheet conformation in the presence of soluble IAPP. Samples are run in the presence and absence (i.e., water alone) of buffering agent, which is done to determine if competitive effects are seen with the ionic buffer (usually phosphate).

A. Assay in Water Only

Add components used at a molar ratio of 1:10 [peptide:compound]; add 10 μ L of 10 mg/mL IAPP stock solution (final 100 μ g peptide) to the aqueous solution containing compound to a final volume of 400 μ L. The pH of the final assay solution is measured to ensure there is no fluctuation and the spectrum is accumulated using the parameters as shown above.

B. Assay in Phosphate Buffer

Add desired amount of compound to achieve a 1:10 molar ratio in 10 mM phosphate buffer, pH 7. Add 10 μ L of 10 mg/mL IAPP stock solution (final peptide 100 μ g) to the phosphate buffered solution containing the compound and bring to a final volume of 400 μ L. The pH of the final assay solution is measured

to ensure there is no fluctuation and the spectrum is accumulated using the parameters as shown above.

In both assays, a control sample is run with each test group. This control contains peptide only in water or buffer at a similar final volume of 400 μ l.

- 5 Spectra for the control are collected initially (first run) and at the end of the test (final run) to ensure that the peptide has not undergone extensive aggregation during the course of the assay. Spectra for the controls are used to compare with the measurements obtained with the treated samples.

CO-INCUBATION:

- 10 Make fresh 1 mg/mL stock solution of IAPP in 10 mM phosphate buffer, pH 7. Add desired amount of compound to achieve a 1:10 molar ratio in 10 mM phosphate buffer, pH 7. Incubate for 3 days at room temperature. Make up to final volume of 400 μ L with 10 mM phosphate buffer, pH 7. The pH of the final assay solution is measured to ensure there is no fluctuation and the spectrum is
- 15 accumulated using the parameters as shown above.

A similar control is run for comparative purposes.

DATA ANALYSIS

- Plots of the spectra (control and treated) are individually assembled and the changes in ellipticity at 218 nm are examined. This minimum is directly correlated
- 20 with the amount of β -sheet present in the sample. Changes in either a positive or negative direction are noted and a relative value ("active" or "not active") assigned to the compound as a measure of activity.

TABLE 1

Compound	Activity
3-(3-hydroxy-1-propyl)amino-1-propanesulfonic acid	Active
DL-2-amino-5-phosphovaleric acid	Active
1,2,3,4-tetrahydroisoquinoline, HCl	Active
cyclohexylsulfamic acid, sodium salt	Active
O-phospho-L-serine	Active
hexafluoroglutaric acid	Active
8-methoxyquinoline-5-sulfonic acid, sodium salt	Active
4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine, sodium salt	Active
3-amino-2-hydroxy-1-propanesulfonic acid	Active
3-dimethylamino-1-propanesulfonic acid	Active

EXAMPLE 3

The synthesis of a compound of the invention, 4-phenyl-1-(3'-sulfopropyl)-
5 1,2,3,6-tetrahydropyridine, in the sodium salt form, is described below.

To a solution of 4-phenylpyridine (15.5 g, 0.1 mol) in acetone (100 mL) was added 1,3-propane sultone (12.2 g, 0.1 mol) at room temperature. The mixture was then heated at reflux temperature overnight. The resultant suspension was cooled to room temperature. The solid was collected by filtration and washed with
10 acetone. To a solution of the solid (31 g) in methanol (500 mL) was added sodium borohydride (10 g, 260 mmol) portionwise, and the mixture was stirred at room temperature for 2 h. Distilled water (50 mL) was added to destroy the excess of sodium borohydride. The mixture was diluted with methanol (200 mL), and neutralized with Amberlite IR-120 ion-exchange resin (H⁺ form, 300 g). A white

precipitate was formed. The precipitate and the resin were removed by filtration and treated with distilled water (400 mL) at ~100 °C. The mixture was filtered and the residual resin was washed with hot distilled water (2 x 200 mL). The filtrates and washings were combined and concentrated to dryness. The residue was co-
5 evaporated with methanol (3 x 200 mL), and then recrystallized from ethanol-water {8:2 (v/v)} to afford 4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine as white crystals (26 g, 93%). The ¹H and ¹³C NMR spectra were in agreement with the structure.

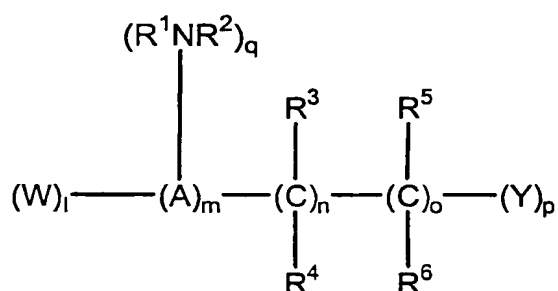
To a solution of 4-phenyl-1-(3'-sulfopropyl)-1,2,3,6-tetrahydropyridine (5.6
10 g, 20 mmol) obtained above in ethanol (180 mL) was added sodium hydroxide (1.2 g, 30 mmol). The suspension was heated at reflux temperature for 30 min. The mixture was then cooled to room temperature. The first crop of product (3.9 g, 64%) was collected by filtration. The filtrate was concentrated to dryness, and the residue was recrystallized from ethanol to afford the second crop of product (2.0 g,
15 32%). ¹H NMR (400 MHz, D₂O): δ 1.85 (quintet, 2 H, J 8.7, 7.7 Hz, 2 H-2'), 2.39–2.45 (m, 4 H, 2 H-3' and 2 H-3), 2.59 (t, 2 H, J 5.6 Hz, 2 H-2), 2.80 (t, 2 H, J 7.7 Hz, 2 H-1'), 3.00 (br s, 2 H, 2 H-6), 6.00 (br s, 1H, H-5), 7.18–7.36 (m, 5 H, Ar). ¹³C NMR (100.6 MHz, D₂O): δ 23.90 (C-2'), 29.01 (C-3), 51.69, 51.76 (C-2, C-3'), 54.45 (C-6), 58.12 (C-1'), 123.75 (C-5), 127.31, 130.01, 131.24 (Ar),
20 136.89 (C-4), 142.47 (Ar).

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this
25 invention and are covered by the following claims. The contents of all references, issued patents, and published patent applications cited throughout this application are hereby incorporated by reference.

CLAIMS

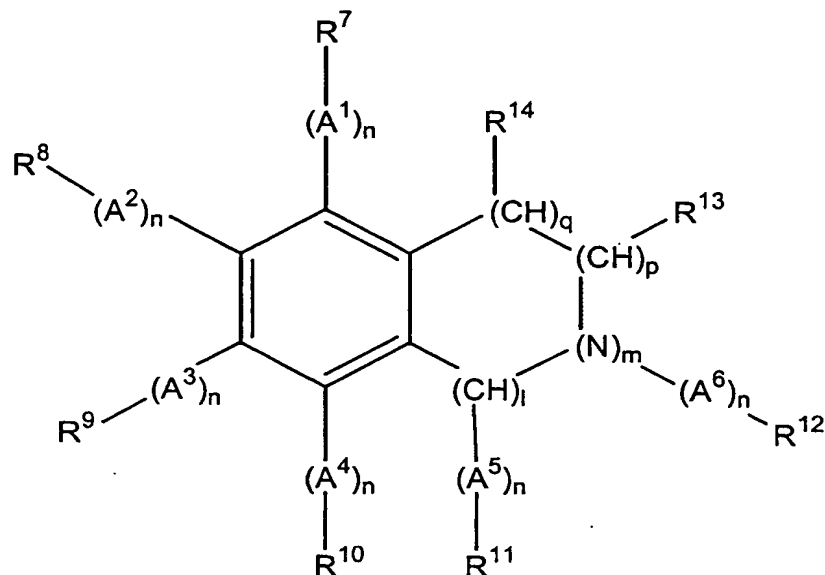
1. A method for inhibiting IAPP-associated amyloid deposits in a subject, comprising administering to said subject an effective amount of an IAPP-inhibiting compound, or a pharmaceutically acceptable ester, acid or salt thereof, such that said IAPP-associated amyloid deposits are inhibited.
2. The method of claim 1 wherein said IAPP-inhibiting compound is of the formula



wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological pH; Y is an anionic group at physiological pH; R^1 and R^2 are independently hydrogen, alkyl, an anionic group at physiological pH, or R^1 and R^2 , taken together with the nitrogen to which they are attached, may form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R^3 is hydrogen, halogen, thiol or hydroxyl; R^4 , R^5 , and R^6 are independently hydrogen or halogen; and A is hydrogen or C_1 to C_6 alkyl; or a pharmaceutically acceptable ester, acid or salt thereof.

3. The method of claim 2, wherein said IAPP inhibiting compound is selected from the group consisting of the compounds depicted in FIGs 10-14, and pharmaceutically acceptable esters, acids or salts thereof.

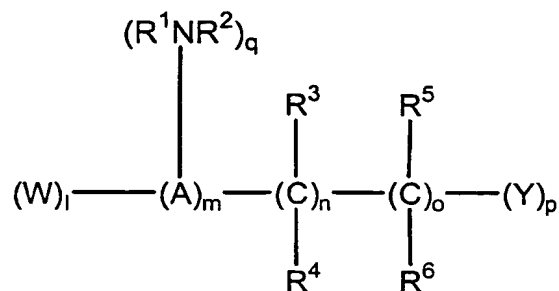
4. The method of claim 1 wherein said IAPP-inhibiting compound is of the formula



wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups may form an unsubstituted or substituted cyclic or heterocyclic ring.

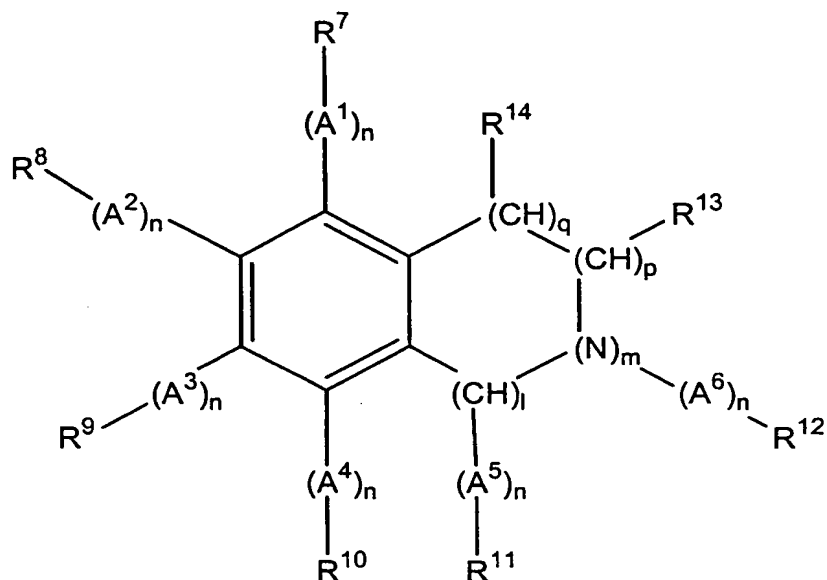
5. The method of claim 4 wherein said compound is selected from the group consisting of 1,2,3,4-tetrahydroisoquinoline, and the compounds depicted in FIGs 1-9.
6. The method of claim 1, wherein said subject has IAPP-associated amyloid deposits in pancreatic islets.
7. A method for inhibiting IAPP fibrillogenesis in a subject, comprising administering to said subject an effective amount of an IAPP inhibiting compound, or a pharmaceutically acceptable ester, acid or salt thereof, such that IAPP fibrillogenesis is inhibited.

8. A pharmaceutical composition for inhibiting IAPP-associated amyloid deposits, comprising an amyloid-inhibiting amount of a therapeutic compound of the formula



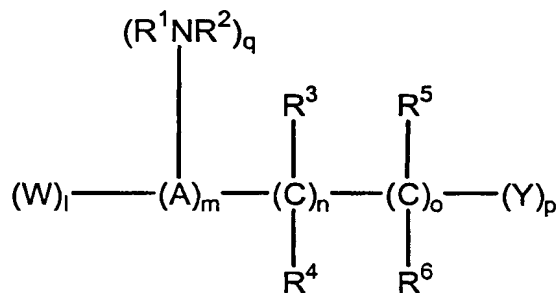
wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological pH; Y is an anionic group at physiological pH; R¹ and R² are independently hydrogen, alkyl, an anionic group at physiological pH, or R¹ and R², taken together with the nitrogen to which they are attached, may form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R³ is hydrogen, halogen, thiol or hydroxyl; R⁴, R⁵, and R⁶ are independently hydrogen or halogen; and A is hydrogen or C₁ to C₆ alkyl; or a pharmaceutically acceptable ester, acid or salt thereof.

9. The pharmaceutical composition of claim 8, wherein said IAPP inhibiting compound is selected from the group consisting of the compounds depicted in FIGs 10-14, and pharmaceutically acceptable esters, acids or salts thereof.
10. A pharmaceutical composition for inhibiting IAPP-associated amyloid deposits, comprising an amyloid-inhibiting amount of a therapeutic compound of the formula



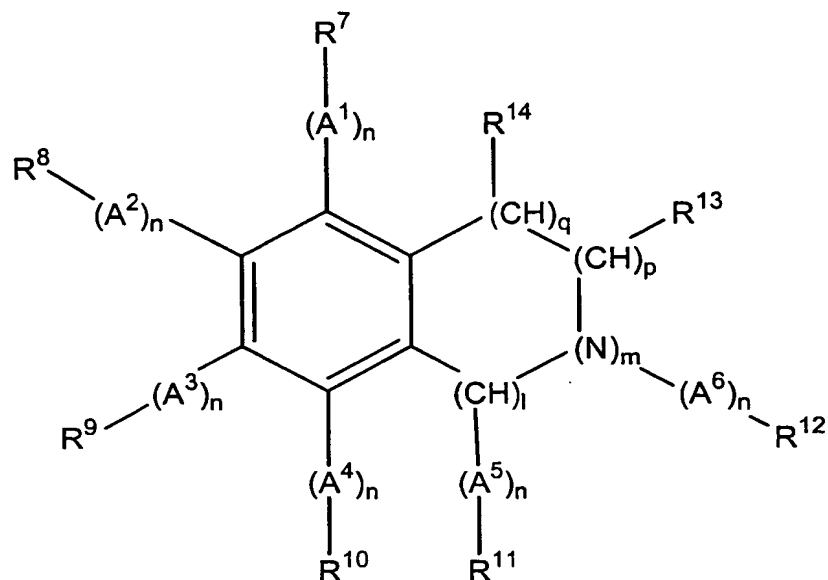
wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups may form an unsubstituted or substituted cyclic or heterocyclic ring.

11. The pharmaceutical composition of claim 10 wherein said compound is selected from the group consisting of the compounds depicted in FIGs 1-9.
12. A method for reducing IAPP-associated amyloid deposits in a subject having IAPP-associated amyloid deposits, the method comprising administering to said subject an effective amount of an IAPP inhibiting compound, or a pharmaceutically acceptable ester, acid or salt thereof, such that said IAPP-associated amyloid deposits are inhibited.
13. The method of claim 12 wherein said IAPP inhibiting compound is of the formula



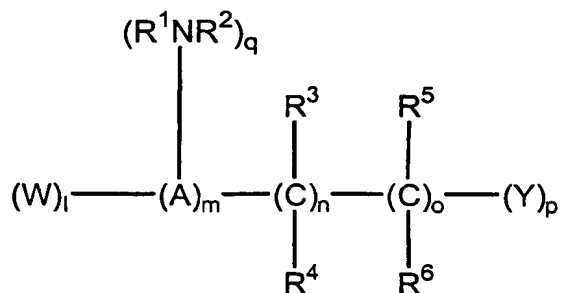
wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological pH; Y is an anionic group at physiological pH; R^1 and R^2 are independently hydrogen, C_1 to C_4 alkyl, an anionic group at physiological pH, or R^1 and R^2 , taken together with the nitrogen to which they are attached, may form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R_3 is hydrogen, halogen, thiol or hydroxyl; R_4 , R_5 , and R_6 are independently hydrogen or halogen; and A is hydrogen or C_1 to C_6 alkyl; or a pharmaceutically acceptable ester, acid or salt thereof.

14. The method of claim 13, wherein said IAPP inhibiting compound is selected from the group consisting of the compounds depicted in FIGs 10-14, and pharmaceutically acceptable esters, acids or salts thereof.
15. The method of claim 12 wherein said IAPP-inhibiting compound is of the formula



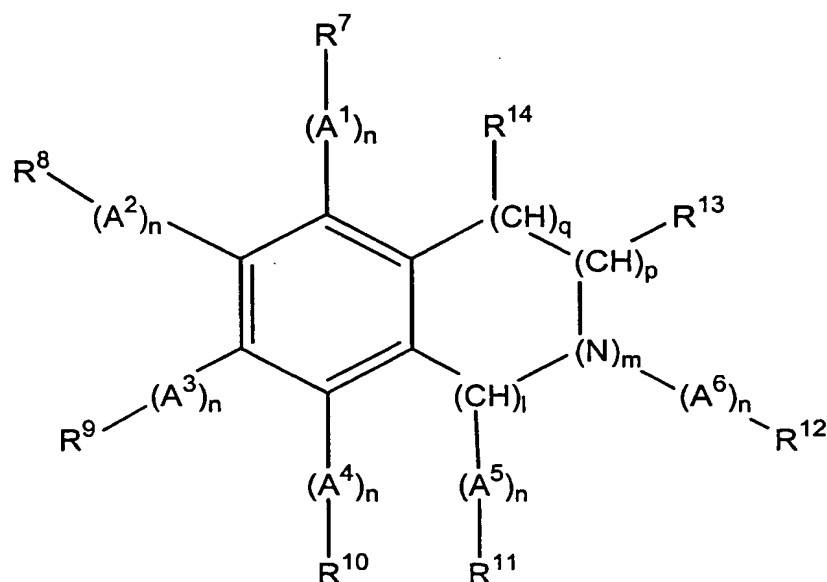
wherein A¹, A², A³, A⁴, A⁵ and A⁶ are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups may form an unsubstituted or substituted cyclic or heterocyclic ring.

16. The method of claim 15 wherein said compound is selected from the group consisting of the compounds depicted in FIGs 1-9.
17. The method of claim 12, wherein said subject has IAPP-associated amyloid deposits in pancreatic islets.
18. A method for inhibiting amyloid deposits in a subject, comprising administering to said subject an effective amount of a compound of the formula



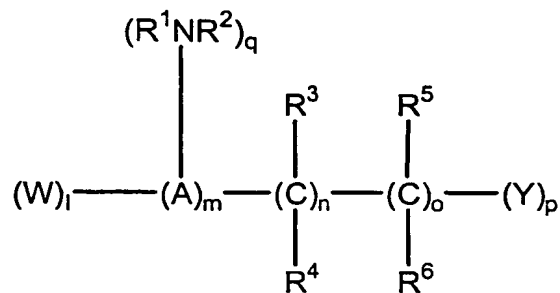
wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological pH; Y is an anionic group at physiological pH; R¹ and R² are independently hydrogen, C₁ to C₄ alkyl, an anionic group at physiological pH, or R¹ and R², taken together with the nitrogen to which they are attached, may form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R₃ is hydrogen, halogen, thiol or hydroxyl; R₄, R₅, and R₆ are independently hydrogen or halogen; and A is hydrogen or C₁ to C₆ alkyl; or a pharmaceutically acceptable ester, acid or salt thereof, such that said amyloid deposits are inhibited.

19. The method of claim 18, wherein said IAPP inhibiting compound is selected from the group consisting of the compounds depicted in FIGs 10-14, and pharmaceutically acceptable esters, acids or salts thereof.
20. A method for inhibiting amyloid deposits in a subject, comprising administering to said subject an effective amount of a compound of the formula



wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups may form an unsubstituted or substituted cyclic or heterocyclic ring, such that said amyloid deposits are inhibited.

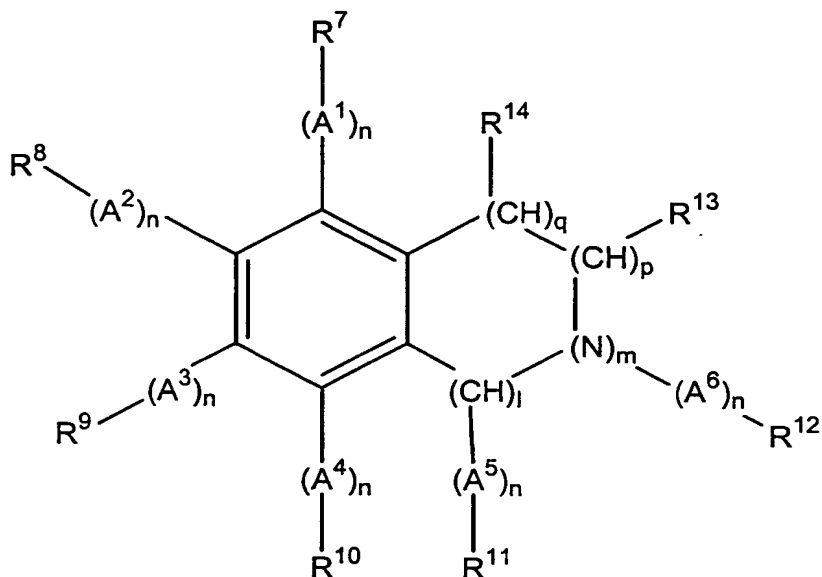
21. The method of claim 20 wherein said compound is selected from the group consisting of the compounds depicted in FIGs 1-9.
- 22.. Use of an IAPP-inhibiting compound, or a pharmaceutically acceptable salt thereof, for treating a disease state characterized by IAPP-associated amyloid deposits.
23. The use of claim 22 wherein said IAPP-inhibiting compound is of the formula



wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological pH; Y is an anionic group at physiological pH; R¹ and R² are independently hydrogen, alkyl, an anionic group at physiological pH, or R¹ and R², taken together with the nitrogen to which they are attached, may form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R³ is hydrogen, halogen, thiol or hydroxyl; R⁴, R⁵, and R⁶ are independently hydrogen or halogen; and A is hydrogen or C₁ to C₆ alkyl; or a pharmaceutically acceptable salt thereof.

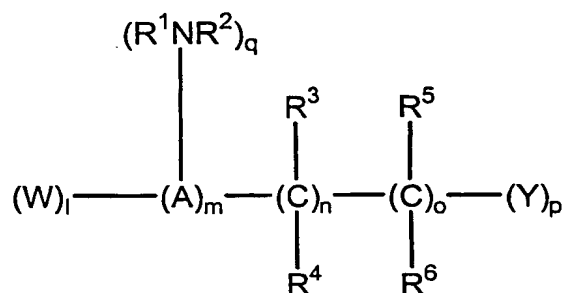
24. The use of claim 23, wherein said IAPP inhibiting compound is selected from the group consisting of the compounds depicted in FIGs 10-14, and pharmaceutically acceptable salts thereof.

25. The use of claim 22 wherein said IAPP-inhibiting compound is of the formula



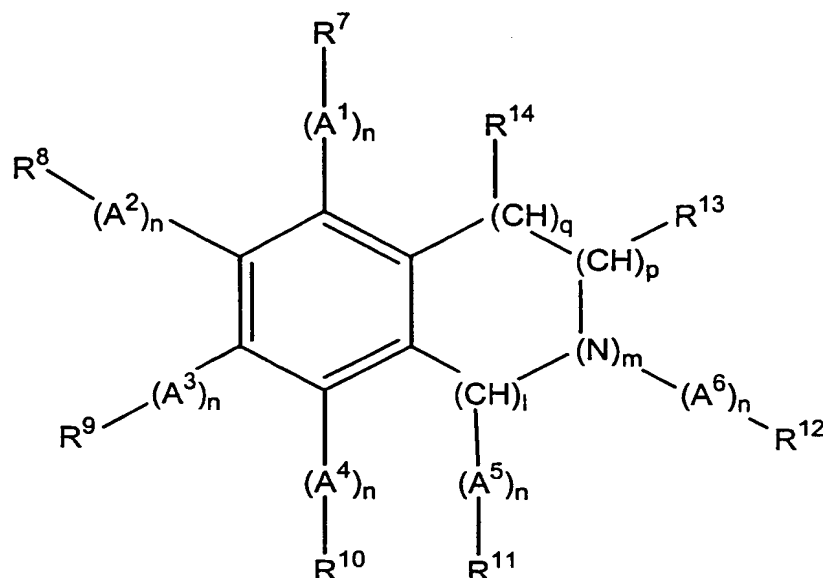
wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups (e.g., R^1 and R^2) may form an unsubstituted or substituted cyclic or heterocyclic ring.

26. The use of claim 25 wherein said compound is selected from the group consisting of 1,2,3,4-tetrahydroisoquinoline, and the compounds depicted in FIGs 1-9.
27. A pharmaceutical composition for inhibiting IAPP-associated amyloid deposits, comprising an amyloid-inhibiting amount of a therapeutic compound of the formula



wherein C is carbon, N is nitrogen, l, m, o, p and q are independently 0 or 1; n is an integer from 0 to 3; W is hydrogen or an anionic group at physiological pH; Y is an anionic group at physiological pH; R^1 and R^2 are independently hydrogen, alkyl, an anionic group at physiological pH, or R^1 and R^2 , taken together with the nitrogen to which they are attached, may form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring; R^3 is hydrogen, halogen, thiol or hydroxyl; R^4 , R^5 , and R^6 are independently hydrogen or halogen; and A is hydrogen or C_1 to C_6 alkyl; or a pharmaceutically acceptable salt thereof.

28. The pharmaceutical composition of claim 27, wherein said IAPP inhibiting compound is selected from the group consisting of the compounds depicted in FIGs 10-14, and pharmaceutically acceptable salts thereof.
29. A pharmaceutical composition for inhibiting IAPP-associated amyloid deposits, comprising an amyloid-inhibiting amount of a therapeutic compound of the formula

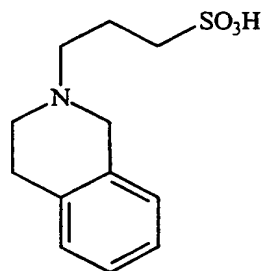


wherein A^1 , A^2 , A^3 , A^4 , A^5 and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; l, p and q are independently 0, 1, or 2; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl or aryl, and adjacent R groups may form an unsubstituted or substituted cyclic or heterocyclic ring.

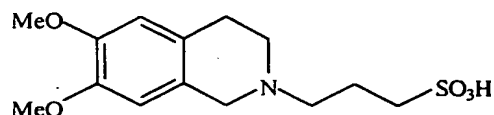
30. The pharmaceutical composition of claim 29 wherein said compound is selected from the group consisting of the compounds depicted in FIGs 1-9.
31. Use of a compound as set forth in any of claims 22-26 in the manufacture of a medicament for treating a disease state characterized by IAPP-associated amyloid deposits.

1 / 14

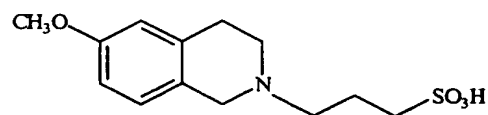
3-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-1-propanesulfonic acid



3-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-1-propanesulfonic acid



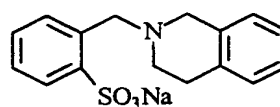
3-[2-(6-Methoxy-1,2,3,4-tetrahydroisoquinolyl)]-1-propanesulfonic acid



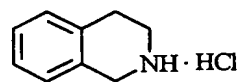
2-(2-Sulfobenzoyl)-1,2,3,4-tetrahydroisoquinoline, sodium salt



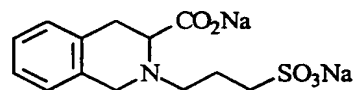
2-(2-Sulfobenzyl)-1,2,3,4-tetrahydroisoquinoline, sodium salt



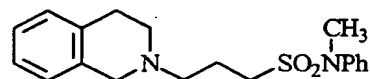
1,2,3,4-Tetrahydroisoquinoline, hydrochloride



3-[2-(3-Carboxy-1,2,3,4-tetrahydroisoquinolyl)]-1-propanesulfonic acid, disodium salt



N-Methyl-*N*-phenyl-3-[2-(1,2,3,4-tetrahydroisoquinolyl)]-1-propanesulfonamide



4-[2-(1,2,3,4-Tetrahydroisoquinolyl)]-1-butanesulfonic acid, sodium salt

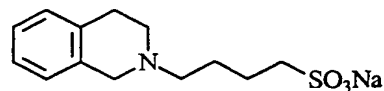
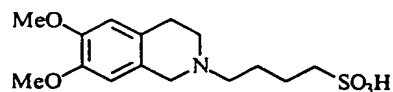


FIG. 1

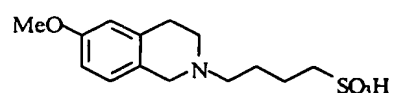
SUBSTITUTE SHEET (RULE 26)

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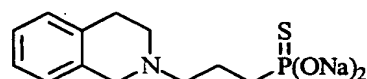
4-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoliny)]-1-butanesulfonic acid



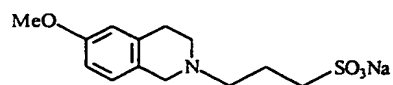
4-[2-(6-methoxy-1,2,3,4-tetrahydroisoquinoliny)]-1-butanesulfonic acid



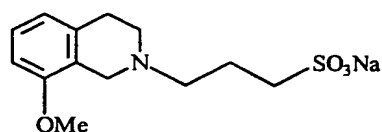
3-[2-(1,2,3,4-Tetrahydroisoquinoliny)]-1-propylthiophosphonic acid, disodium salt



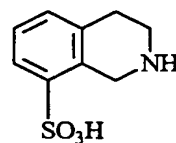
3-[2-(6-Methoxy-1,2,3,4-tetrahydroisoquinoliny)]-1-propanesulfonic acid, sodium salt



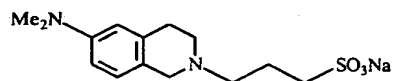
3-[2-(8-Methoxy-1,2,3,4-tetrahydroisoquinoliny)]-1-propanesulfonic acid, sodium salt



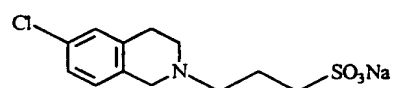
1,2,3,4-Tetrahydro-8-isoquinolinesulfonic acid



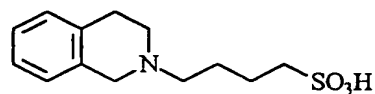
3-[2-(6-Dimethylamino-1,2,3,4-tetrahydroisoquinoliny)]-1-propanesulfonic acid, sodium salt



3-[2-(6-Chloro-1,2,3,4-tetrahydroisoquinoliny)]-1-propanesulfonic acid, sodium salt -



4-[2-(1,2,3,4-Tetrahydroisoquinoliny)]-1-butanesulfonic acid



1,2,3,4-Tetrahydro-5-isoquinolinesulfonic acid

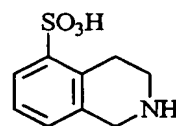
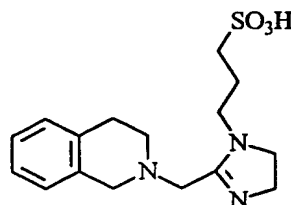


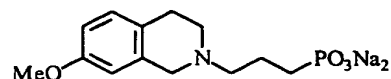
FIG. 2

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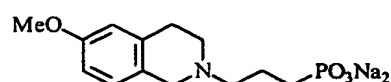
1-Sulfopropyl-2-[2-(1,2,3,4-tetrahydroisoquinoliny)methyl]-4,5-dihydroimidazole



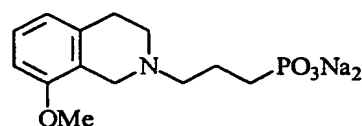
3-[7-Methoxy-2-(1,2,3,4-tetrahydroisoquinoliny)]propylphosphonic acid, disodium salt



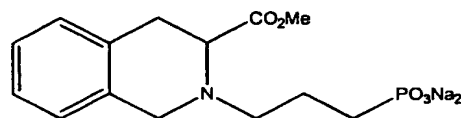
3-[6-Methoxy-2-(1,2,3,4-tetrahydroisoquinoliny)]propylphosphonic acid, disodium salt



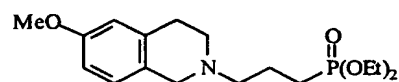
3-[8-Methoxy-2-(1,2,3,4-tetrahydroisoquinoliny)]propylphosphonic acid, disodium salt



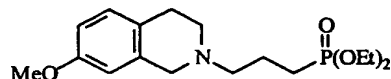
3-[2-(3-Methoxycarbonyl-1,2,3,4-tetrahydroisoquinoliny)]propylphosphonic acid, disodium salt



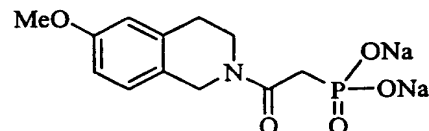
3-[6-Methoxy-2-(1,2,3,4-tetrahydroisoquinoliny)]propylphosphonic acid, diethyl ester



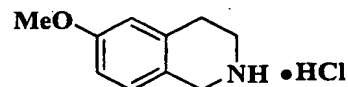
3-[7-Methoxy-2-(1,2,3,4-tetrahydroisoquinoliny)]propylphosphonic acid, diethyl ester



N-Phosphonoacetyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline, disodium salt



6-Methoxy-1,2,3,4-tetrahydroisoquinoline, hydrochloride



N-Sulfoacetyl-1,2,3,4-tetrahydroisoquinoline, sodium salt

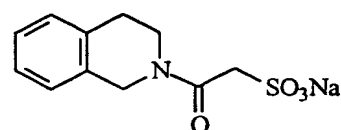
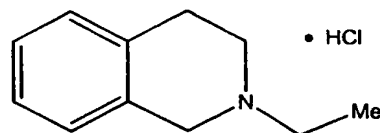


FIG. 3

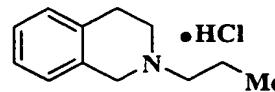
SUBSTITUTE SHEET (RULE 26)

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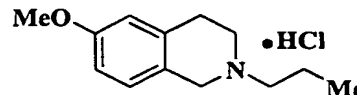
N-Ethyl-1,2,3,4-tetrahydroisoquinoline, hydrochloride



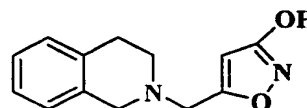
N-Propyl-1,2,3,4-tetrahydroisoquinoline, hydrochloride



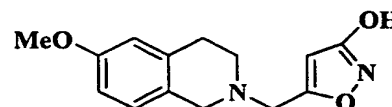
N-Propyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline, hydrochloride



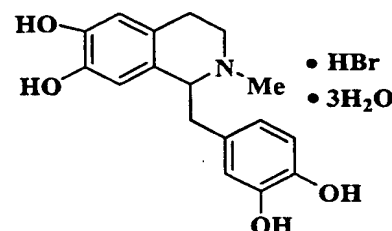
5-[(1,2,3,4-Tetrahydroisoquinol-2-yl)methyl]isoxazol-3-ol



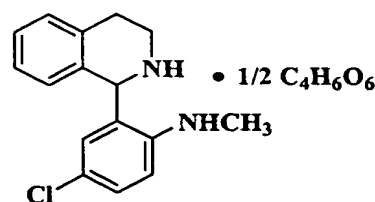
5-[(6-Methoxy-1,2,3,4-tetrahydroisoquinol-2-yl)methyl]isoxazol-3-ol



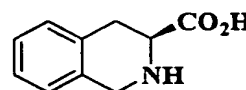
(±)-Laudanosoline hydrobromide trihydrate



(-)-1-[5-Chloro-2-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (-)-tartrate



(*S*)-(-)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid



Tetrahropapaveroline hydrobromide (Norlaudanoline hydrobromide)

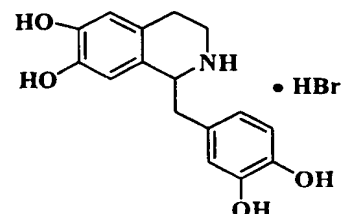
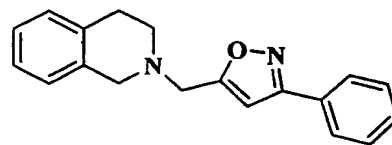


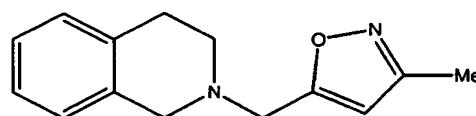
FIG. 4

SUBSTITUTE SHEET (RULE 26)

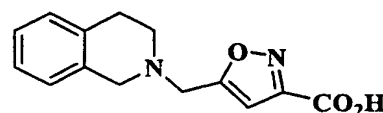
3-phenyl-5-[2-(1,2,3,4-tetrahydroisoquinolyl)methyl]isoxazole



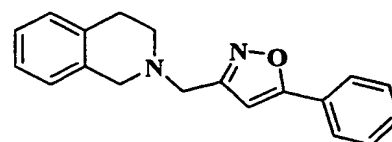
3-Methyl-5-[2-(1,2,3,4-tetrahydroisoquinolyl)methyl]isoxazole



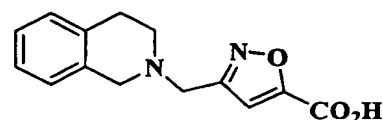
5-[2-(1,2,3,4-Tetrahydroisoquinolyl)methyl]isoxazole-3-carboxylic acid



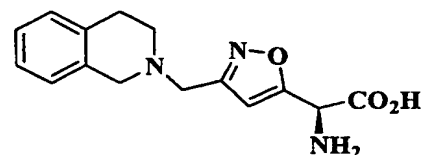
5-phenyl-3-[2-(1,2,3,4-tetrahydroisoquinolyl)methyl]isoxazole



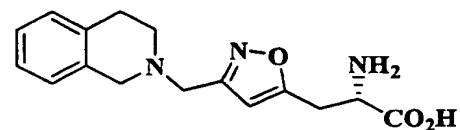
3-[2-(1,2,3,4-Tetrahydroisoquinolyl)methyl]isoxazole-5-carboxylic acid



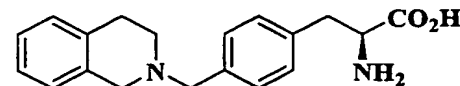
(2S)-2-Amino-2-[3-(2-1,2,3,4-tetrahydroisoquinolylmethyl)isoxazol-5-yl]acetic acid



3-[2-(1,2,3,4-Tetrahydroisoquinolyl)-methyl]isoxazole-5-L-alanine



4-[2-(1,2,3,4-Tetrahydroisoquinolyl)methyl]-L-phenylalanine



5-[2-(1,2,3,4-Tetrahydroisoquinolyl)methyl]-1H-1,2,3,4-tetrazole

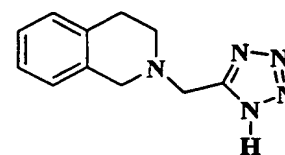
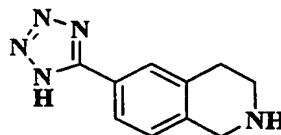
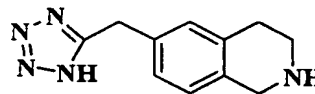
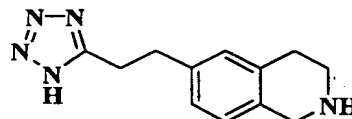
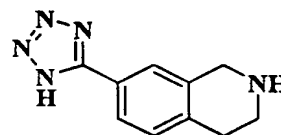
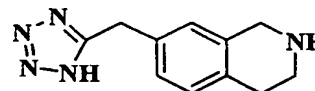
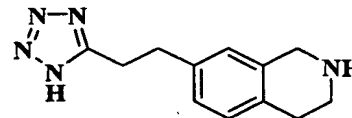


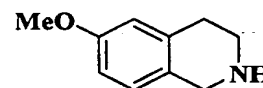
FIG. 5

SUBSTITUTE SHEET (RULE 26)

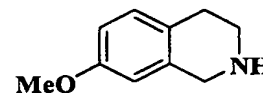
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5-(1,2,3,4-Tetrahydroisoquinol-6-yl)-1*H*-1,2,3,4-tetrazole5-[6-(1,2,3,4-Tetrahydroisoquinolyl)methyl]-1*H*-1,2,3,4-tetrazole5-{2-[6-(1,2,3,4-Tetrahydroisoquinolyl)]ethyl}-1*H*-1,2,3,4-tetrazole5-(1,2,3,4-Tetrahydroisoquinol-7-yl)-1*H*-1,2,3,4-tetrazole5-[7-(1,2,3,4-Tetrahydroisoquinolyl)methyl]-1*H*-1,2,3,4-tetrazole5-{2-[7-(1,2,3,4-Tetrahydroisoquinolyl)]ethyl}-1*H*-1,2,3,4-tetrazole

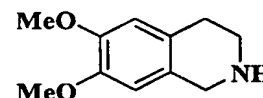
6-Methoxy-1,2,3,4-tetrahydroisoquinoline



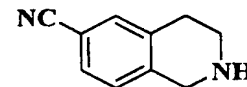
7-Methoxy-1,2,3,4-tetrahydroisoquinoline



6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline



1,2,3,4-Tetrahydroisoquinoline-6-carbonitrile



1,2,3,4-tetrahydroisoquinoline-7-carbonitrile

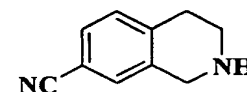
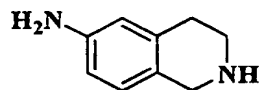


FIG. 6

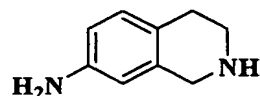
SUBSTITUTE SHEET (RULE 26)

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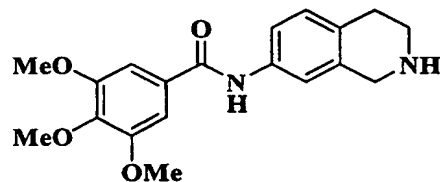
6-Amino-1,2,3,4-tetrahydroisoquinoline



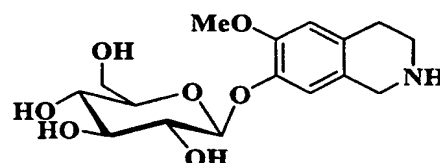
7-Amino-1,2,3,4-tetrahydroisoquinoline



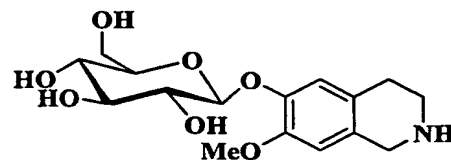
7-(3,4,5-Trimethoxybenzoyl)amino-1,2,3,4-tetrahydroisoquinoline



7-β-D-Glucopyranosyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline



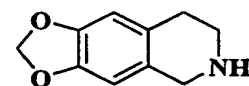
6-β-D-Glucopyranosyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline



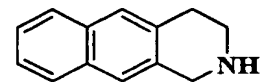
(1,2,3,4-Tetrahydroisoquinol-1-yl)phosphonic acid



5,6,7,8-Tetrahydro-2H-1,3-dioxoleno[4,5-g]isoquinoline



1,2,3,4-Tetrahydrobenzo[g]isoquinoline



(1,2,3,4-Tetrahydroisoquinol-7-ylsulfonyl)aminobenzene

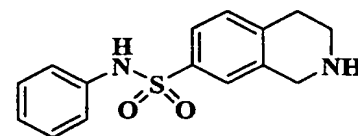
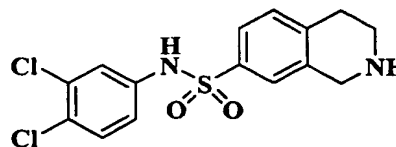


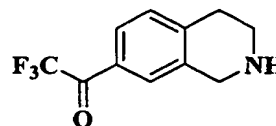
FIG. 7

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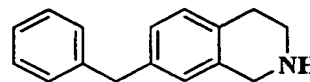
1-[(1,2,3,4-Tetrahydroisoquinol-7-ylsulfonyl)amino]-3,4-dichlorobenzene



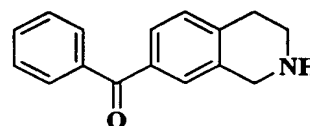
7-(2,2,2-Trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline



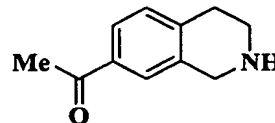
7-Benzyl-1,2,3,4-tetrahydroisoquinoline



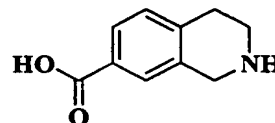
7-Benzoyl-1,2,3,4-tetrahydroisoquinoline



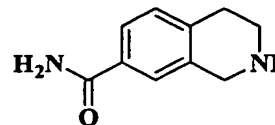
7-Acetyl-1,2,3,4-tetrahydroisoquinoline



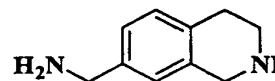
1,2,3,4-Tetrahydroisoquinoline-7-carboxylic acid



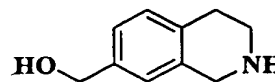
1,2,3,4-Tetrahydroisoquinoline-7-carboxamide



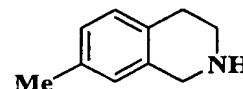
7-Aminomethyl-1,2,3,4-tetrahydroisoquinoline



7-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline



7-Methyl-1,2,3,4-tetrahydroisoquinoline



7-hydroxy-1,2,3,4-tetrahydroisoquinoline

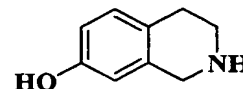
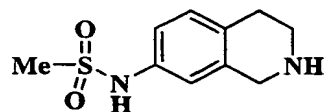


FIG. 8

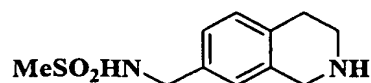
SUBSTITUTE SHEET (RULE 26)

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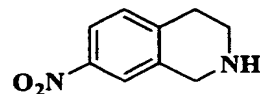
7-(Methanesulfonyl)amino-1,2,3,4-tetrahydroisoquinoline



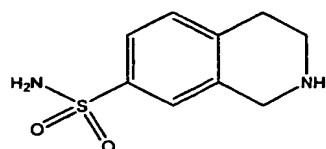
7-(Methanesulfonyl)aminomethyl-1,2,3,4-tetrahydroisoquinoline



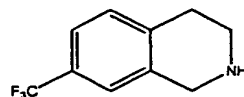
7-Nitro-1,2,3,4-tetrahydroisoquinoline



1,2,3,4-Tetrahydroisoquinoline-7-sulfonamide



7-Trifluoromethyl-1,2,3,4-tetrahydroisoquinoline



7-Methylthio-1,2,3,4-tetrahydroisoquinoline

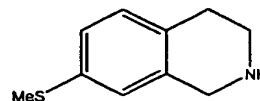
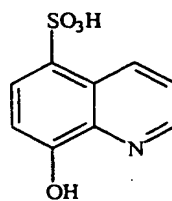


FIG. 9

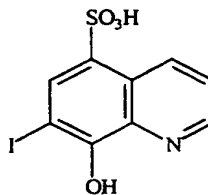
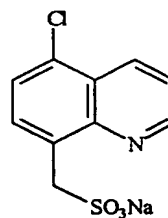
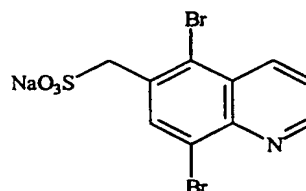
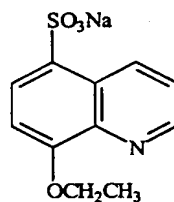
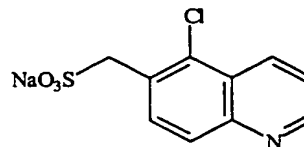
SUBSTITUTE SHEET (RULE 26)

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8-hydroxy-5-quinolinesulfonic acid



8-hydroxy-7-iodo-5-quinolinesulfonic acid

5-Chloro-8-quinolylmethylsulfonic acid,
sodium salt5,8-Dibromo-6-quinolylmethylsulfonic acid,
sodium salt8-Ethoxy-5-quinolinesulfonic acid, sodium
salt5-Chloro-6-quinolylmethylsulfonic acid,
sodium salt

Quinoline yellow

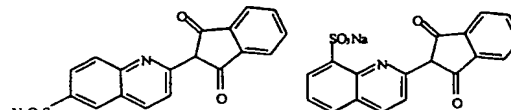
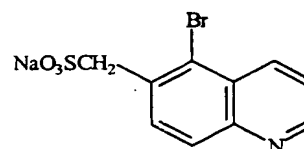
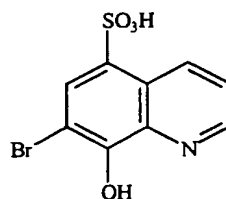
5-Bromo-6-quinolylmethylsulfonic acid,
sodium salt

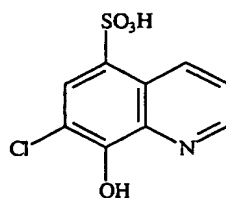
FIG. 10

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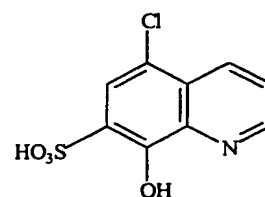
7-Bromo-8-hydroxy-5-quinolinesulfonic acid



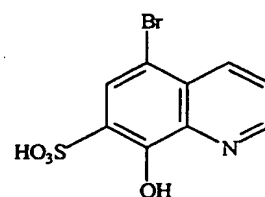
7-Chloro-8-hydroxy-5-quinolinesulfonic acid



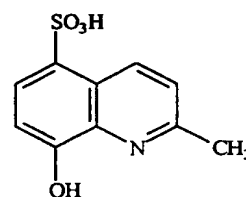
5-Chloro-8-hydroxy-7-quinolinesulfonic acid



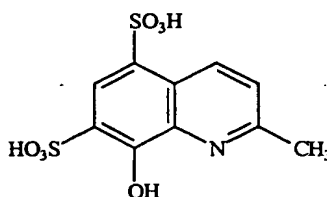
5-Bromo-8-hydroxy-7-quinolinesulfonic acid



8-hydroxy-2-methyl-5-quinolinesulfonic acid



8-hydroxy-2-methyl-5,7-quinolinedisulfonic acid



5-Chloro-8-hydroxy-2-methyl-7-quinolinesulfonic acid

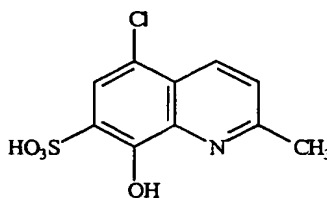
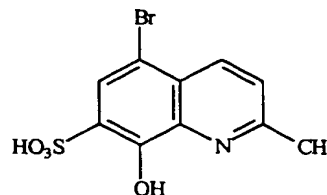


FIG. 11

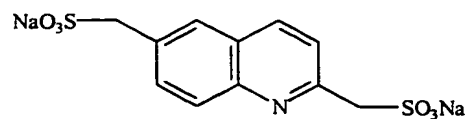
SUBSTITUTE SHEET (RULE 26)

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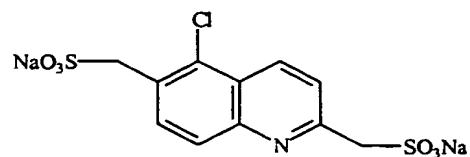
5-Bromo-8-hydroxy-2-methyl-7-quinolinesulfonic acid



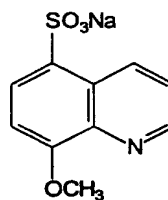
2,6-Quinolyldimethyldisulfonic acid, disodium salt



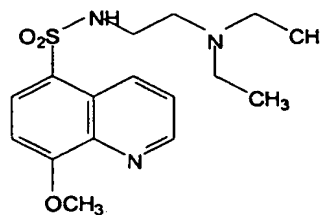
5-Chloro-2,6-quinolyldimethyldisulfonic acid, disodium salt



8-methoxy-5-quinolinesulfonic acid, sodium salt



8-Methoxy-5-[N-(2-N',N'-diethylethylamino)]quinolinesulfonamide



8-Methoxy-5-[N-(2-N',N'-indolineethylamino)]quinolinesulfonamide

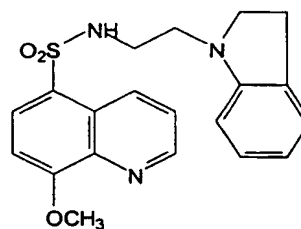
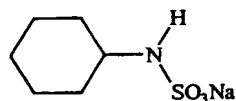


FIG. 12

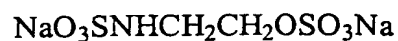
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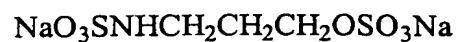
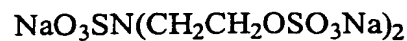
Cyclohexylsulfamic acid, sodium salt



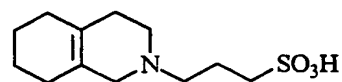
2-hydroxyethylsulfamic acid sulfate, disodium salt



3-hydroxypropylsulfamic acid sulfate, disodium salt

*N,N*-Bis(2-hydroxyethyl)sulfamic acid disulfate, disodium salt

3-[2-(1,2,3,4,5,6,7,8-Octahydroisoquinoliny)]-1-propanesulfonic acid



4-[2-(1,2,3,4,5,6,7,8-Octahydroisoquinoliny)]-1-butanesulfonic acid

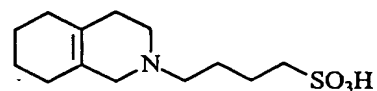
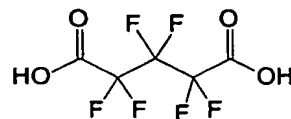


FIG. 13

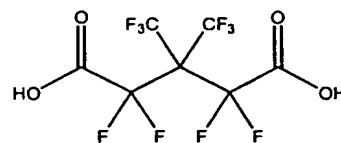
SUBSTITUTE SHEET (RULE 26)

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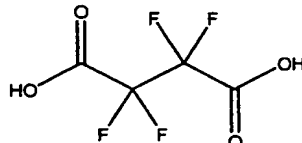
Hexafluoroglutaric acid



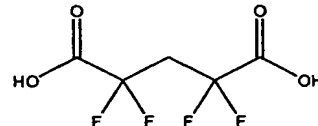
3,3-bis(trifluoromethyl)-2,2,4,4-tetrafluoro-1,5-pentanedioic acid



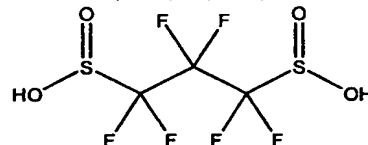
2,2,3,3-tetrafluoro-1,4-butanedioic acid



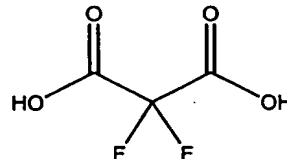
2,2,4,4-tetrafluoro-1,5-pentanedioic acid



hexafluoro-1,3-propanedisulfinic acid



2,2-difluoro-1,3-propanedioic acid



3-hydroxyl-2,2,4,4,4-pentafluoro-3-phenylbutanoic acid

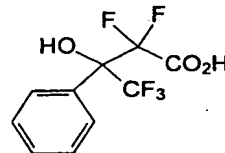


FIG. 14

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International Bureau



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30 November 2000 (30.11.2000)

PCT

(10) International Publication Number
WO 00/71101 A3

(51) International Patent Classification⁷: **A61K 31/00**,
31/472, 31/675, 31/4725, 31/706, 31/4741, 31/473, 31/47,
31/4709, 31/185, 31/194, 31/192, A61P 43/00

(74) Agents: COTE, France et al.: Swabey Ogilvy Renault,
Suite 1600, 1981 McGill College Avenue, Montreal,
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(21) International Application Number: PCT/CA00/00607

(22) International Filing Date: 24 May 2000 (24.05.2000)

(25) Filing Language: English

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(30) Priority Data:
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60/143,123 9 July 1999 (09.07.1999) US
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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
6 December 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND COMPOUNDS FOR INHIBITING AMYLOID DEPOSITS

(57) Abstract: Methods and compositions which are useful in the treatment of amyloidosis. In particular, methods and compositions are provided for inhibiting, preventing and treating amyloid deposition, e.g., in pancreatic islets, wherein the amyloidotic deposits are islet amyloid polypeptide (IAPP)-associated amyloid deposition or deposits. The methods of the invention involve administering to a subject a therapeutic compound which inhibits IAPP-associated amyloid deposits. Accordingly, the compositions and methods of the invention are useful for inhibiting IAPP-associated amyloidosis in disorders in which such amyloid deposition occurs, such as diabetes.



WO 00/71101 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00607

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/472 A61K31/675 A61K31/4725 A61K31/706
A61K31/4741 A61K31/473 A61K31/47 A61K31/4709 A61K31/185
A61K31/194 A61K31/192 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 03680 A (FRASER PAUL ;NEUROCHEM INC (CA); SZAREK WALTER (CA); WEAVER DONALD) 18 January 2001 (2001-01-18) abstract; claims; examples ---	1-31
E	WO 00 64420 A (KONG XIANQI ;NEUROCHEM INC (CA); SZAREK WALTER (CA); UNIV KINGSTON) 2 November 2000 (2000-11-02) abstract page 2, line 15 -page 4, line 25 page 12, line 17 -page 16, line 13 page 22, line 21 -page 23, line 5; claims 1-11,37-53; figures; examples 6,7,9 --- -/--	1-31



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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- "P" document published prior to the international filing date but later than the priority date claimed

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- "&" document member of the same patent family

Date of the actual completion of the international search

2 May 2001

Date of mailing of the international search report

2 5. 05. 01

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Fax: (+31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00607

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 00 57707 A (PROTEOTECH INC) 5 October 2000 (2000-10-05)</p> <p>abstract page 1, line 1 -page 2, line 9 page 3, line 4 -page 4, line 3 page 5, line 19 - line 24; claims 1,11,12,14; example 6</p> <p style="text-align: center;">---</p>	<p>1,6,7, 12,17, 22,31</p>
P,X	<p>WO 00 06133 A (NEUROCHEM INC ;UNIV KINGSTON (CA)) 10 February 2000 (2000-02-10)</p> <p>abstract page 2, line 8 -page 4, line 30 page 42 page 48 -page 49; claims; figures 1-4,10</p> <p style="text-align: center;">---</p>	<p>8-11, 27-30</p>
X	<p>WO 96 28187 A (KISILEVSKY ROBERT ;SZAREK WALTER (CA); UNIV KINGSTON (CA); WEAVER) 19 September 1996 (1996-09-19)</p> <p>the whole document, in particular page 20, lines 15-27; figure 10, compounds XXVII,XXX,XXXII</p> <p style="text-align: center;">---</p>	<p>1-3,6-9, 12-14, 17-19, 22-24, 27,28,31</p>
X	<p>POWELL D S (REPRINT) ET AL: "Insulin and polyionic sulphonates modify human islet amyloid polypeptide fibril aggregation in vitro" DIABETOLOGIA, (AUG 1998) VOL. 41, SUPP. [1], PP. 656-656. PUBLISHER: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0012-186X., XP000978398 RADCLIFFE INFIRM, DIABET RES LABS, OXFORD OX2 6HE, ENGLAND;UNIV OXFORD, DEPT HUMAN ANAT, OXFORD OX1 3QX, ENGLAND; UNIV TORONTO, CNDR, TORONTO, ON, CANADA; QUEENS UNIV, DEPT CHEM, KINGSTON, ON K7L 3N6, CANADA the whole document</p> <p style="text-align: center;">---</p>	<p>1,6,7, 12,17, 22,31</p>
X	<p>WO 94 22437 A (UNIV KINGSTON) 13 October 1994 (1994-10-13)</p> <p>the whole document, in particular page 15, lines 21-33</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1,6,7, 12,17, 22,31</p>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00607

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 164 295 A (KISILEVSKY ROBERT ET AL) 17 November 1992 (1992-11-17) abstract column 1, line 1 - line 53 column 2, line 10 - line 44 column 7, line 25 - line 41; claim 1 ---	1,6,7, 12,17, 22,31
X	WO 97 09976 A (UNIV WASHINGTON) 20 March 1997 (1997-03-20) abstract page 2, line 27 - line 34; claims 1-4 ---	8,9,27, 28
A	WO 96 37612 A (PFIZER ;CARTY MAYNARD D (US); KREUTTER DAVID K (US); SOELLER WALTE) 28 November 1996 (1996-11-28) page 1, line 1 - line 22 page 3, line 18 - line 26; claims 25-31; figures 6,7 ---	1-3,6-9, 12-14, 17-19, 22-24, 27,28,31
A	O'BRIEN T D ET AL: "HUMAN ISLET AMYLOID POLYPEPTIDE EXPRESSION IN COS-1 CELLS A MODEL OF INTRACELLULAR AMYLOIDOGENESIS" AMERICAN JOURNAL OF PATHOLOGY,US,PHILADELPHIA, PA, vol. 147, no. 3, 1 September 1995 (1995-09-01), pages 609-616, XP000590832 ISSN: 0002-9440 the whole document ---	1-3,6-9, 12-14, 17-19, 22-24, 27,28,31
X	DE 43 13 118 A (HOECHST AG) 27 October 1994 (1994-10-27) the whole document ---	10,11,29
X	GEORGIEV, V. S. ET AL: "Drug-induced modifications of the immune response. 1. Substituted 1-phenylisoquinolines" J. MED. CHEM. (1979), 22(4), 348-52 , XP000992891 the whole document, in particular compound 25 ---	10,11, 29,30
X	US 3 872 125 A (HOULIHAN WILLIAM J ET AL) 18 March 1975 (1975-03-18) the whole document ---	10,29
A		4,5,15, 16,20, 21,25,26

	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/00607

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 236 251 A (UNIV PASTEUR) 9 September 1987 (1987-09-09)	10,29
A	abstract; claims 1,10,17; examples	4,5,15, 16,20, 21,25,26
A	<p>---</p> <p>BAURES, PAUL W. ET AL: "Discovering transthyretin amyloid fibril inhibitors by limited screening"</p> <p>BIOORG. MED. CHEM. (1998), 6(8), 1389-1401</p> <p>' XP002129747</p> <p>abstract; figure 1</p> <p>---</p>	4,5,15, 16,20, 21,25,26
A	<p>---</p> <p>MALMUSI L ET AL:</p> <p>"1,2,3,4-TETRAHYDROISOQUINOLINE AND RELATED ANALOGS OF THE PHENYLALKYLAMINE DESIGNER DRUG MDMA"</p> <p>MEDICINAL CHEMISTRY RESEARCH, BIRKHAUSER, BOSTON, US,</p> <p>vol. 6, no. 6, 1996, pages 412-426,</p> <p>XP000978322</p> <p>ISSN: 1054-2523</p> <p>abstract; table 2</p> <p>-----</p>	10,11, 29,30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00607

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7,12-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1(partially),2,3,6(partially),7(partially),8,9,12(partially),
13,14,17(partially),18,19,22(partially),23,24,27,28,31(partially)

Method for inhibiting IAPP-associated amyloid deposits with an
IAPP-inhibiting compound such as defined in claims 2-3 and composition
thereof.

2. Claims: 1(partially),4,5,6(partially),7(partially),10,11,12(partially),
15,16,17(partially),20,21,22(partially),25,26,29,30,31(partially)

Method for inhibiting IAPP-associated amyloid deposits with an
an IAPP-inhibiting compound such as defined in claims 4-5 and composition
thereof

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,6,7,12,17,22,31 relate to a compound defined by reference to a desirable characteristic or property, namely "IAPP-inhibiting compound".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, present claims 2,4,8,10,13,15,18,20,23,25,27,29 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in FIGs 1-14, and to 1,2,3,4-tetrahydroisoquinoline derivatives, with due regard to the general idea underlying the present invention.

Claims searched completely: 3,5,9,11,14,16,19,21,24,26,28,30

Claims searched incompletely:

1-2,4,6-8,10,12,13,15,17,18,20,22,23,25,27,29,31

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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